FORM PTO-1390 (Modified) (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
P24,002 USA	
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5)	
09/529537	
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE
PCT/GB98/03076	12 October 1998 (12.10.98)
PRIORITY DATE CLAIMED	
15 October 1997 (15.10.97)	

TITLE OF INVENTION
ANALGESIC COMPOSITIONS

APPLICANT(S) FOR DO/EO/US
Leslie Lars IVERSEN

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
    A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☒ Certificate of Mailing by Express Mail
19. ☒ Other items or information:
    - **Cover Page of Published International Application WO 99/18967**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/529537	PCT/GB98/03076	P24,002 USA

20. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		CALCULATIONS PTO USE ONLY
☒ Search Report has been prepared by the EPO or JPO	$840.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482)	$670.00	
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	$760.00	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO	$970.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$96.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =				$840.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).				$130.00
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	20 - 20 =	0	x $18.00	$0.00
Independent claims	2 - 3 =	0	x $78.00	$0.00
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00
TOTAL OF ABOVE CALCULATIONS			=	$970.00
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**.			☐	$0.00
SUBTOTAL			=	$970.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	$0.00
TOTAL NATIONAL FEE			=	$970.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	$0.00
TOTAL FEES ENCLOSED			=	$970.00
			Amount to be: refunded	$
			charged	$

☒ A check in the amount of **$970.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **19-5425** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Alexis Barron, Esquire
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Fascimile No. (215) 923-2189

SIGNATURE

Alexis Barron
NAME

22,702
REGISTRATION NUMBER

April 14, 2000
DATE

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) AND 1.27 (c)) - SMALL BUSINESS CONCERN	Docket No. 24,002 USA

Serial No.	Filing Date	Patent No.	Issue Date
09/529,537	14 April 2000		

Applicant/
Patentee: **Leslie Lars IVERSEN**

Invention: **ANALGESIC COMPOSITION**

I hereby declare that I am:

- ☐ the owner of the small business concern identified below:
- ☒ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN: **Panos Therapeutics Limited**
ADDRESS OF CONCERN: **The Doctor's House, High Street, Little Milton, Oxford, OX44 7PU, ENGLAND**

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the above identified invention described in:

- ☐ the specification filed herewith with title as listed above.
- ☒ the application identified above.
- ☐ the patent identified above.

If the rights held by the above-identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed on the next page and no rights to the invention are held by any person, other than the inventor, who could not qualify as an independent inventor under 37 CFR 1.9(c) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

- ☐ no such person, concern or organization exists.
- ☐ each such person, concern or organization is listed below.

FULL NAME _____
ADDRESS _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

FULL NAME _____
ADDRESS _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

FULL NAME _____
ADDRESS _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

FULL NAME _____
ADDRESS _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: DR. LESLIE LARS JIERSEN

TITLE OF PERSON SIGNING OTHER THAN OWNER: DIRECTOR

ADDRESS OF PERSON SIGNING: **Panos Therapeutics Limited**
The Doctor's House, High Street, Little Milton
Oxford, OX44 7PU, ENGLAND

SIGNATURE: Leslie Jiersen DATE: 4TH JUNE 2000

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April 14, 2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of Leslie Lars IVERSEN
Based on International Application No. PCT/GB98/03076
U.S. Application No. Not Yet Assigned
Filed Herewith on April 14, 2000
ANALGESIC COMPOSITIONS (Atty. Docket No. 24,002 USA)

CERTIFICATE OF EXPRESS MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service on this date, April 14, 2000, in an envelope as "Express Mail Post Office to Addressee," Mailing Label No. EL389265115USA addressed to the Assistant Commissioner for Patents, Box PCT, Washington, D.C. 20231 ATTN: DO/EO/US.

Mary K. Clancy

Assistant Commissioner for Patents
Box PCT
Washington, D.C. 20231
ATTN: DO/EO/US

PRELIMINARY AMENDMENT REDUCING THE NUMBER OF CLAIMS PRIOR TO CALCULATION OF THE FILING FEE AND ACCOMPANYING REQUEST TO BEGIN NATIONAL EXAMINATION UNDER 35 USC §371(f)

Sir:

Please cancel Claims 3 to 20 inclusive without prejudice.

Respectfully Submitted,
SYNNESTVEDT & LECHNER LLP

Alexis Barron
(Registration No. 22,702)

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April 14, 2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of Leslie Lars IVERSEN
Based on International Application No. PCT/GB98/03076
U.S. Application No. Not Yet Assigned
Filed Herewith on April 14, 2000
ANALGESIC COMPOSITIONS

(Atty. Docket No. 24,002 USA)

CERTIFICATE OF EXPRESS MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service on this date, April 14, 2000, in an envelope as "Express Mail Post Office to Addressee," Mailing Label No. EL389265115US, addressed to the Assistant Commissioner for Patents, Box PCT, Washington, D.C. 20231 ATTN: DO/EO/US.

Mary K. Clancy

Assistant Commissioner for Patents
Box PCT
Washington, D.C. 20231
ATTN: DO/EO/US

SECOND PRELIMINARY AMENDMENT SUBMITTED PRIOR TO FIRST EXAMINATION AND ACTION UNDER 37 CFR §1.115

Sir:

Applicant requests entry of the following amendments.

In the Claims

Please add Claims 21 to 28 as follows.

- - 21. A pharmaceutical formulation according to Claim 1, wherein the organic phase comprises an oil selected from soya bean, safflower, sesame,

rapeseed, peanut, olive, cotton seed and fish oils, alone or in combination with glycerine and/or a wax selected from full and/or partial triglycerides of fatty acids.

22. A pharmaceutical formulation according to Claim 1 intended for intravenous use, wherein the hydrophilic phase is aqueous and has a viscosity of from 2500-7500cp at 20°C.

23. A pharmaceutical formulation according to Claim 1 intended for use as a solid formulation, wherein the hydrophilic phase is gel forming, incorporates the opioid in the gel and forms a matrix incorporating the CCK antagonist and the glyceride derivative.

24. A pharmaceutical formulation according to Claim 1, wherein the hydrophilic phase comprises a pharmacologically and pharmaceutically acceptable polymer or salt thereof selected from proteins such as gelatine, hyaluronic acid, alginic acids or salts thereof such as sodium alginate, carboxymethylcellulose (optionally cross-linked), methyl cellulose, other cellulose derivatives which are water-swellable such as hydroxypropylmethylcellulose and hydroxyethyl-cellulose or other water-swellable polymers such as polyvinyl pyrrolidone (PVP) or water-soluble polymers such as lactose.

25. A pharmaceutical formulation according to Claim 1, wherein the carrier is in the form of an oil-in-water emulsion.

26. A pharmaceutical formulation according to Claim 25, wherein the oil-in-water emulsion comprises

(I) an oil phase comprising a glyceride derivative; and

(ii) an aqueous phase optionally comprising a buffer whereby the emulsion has a pH of from 6.5 to 7.5 and optionally comprises an isotonicty regulator whereby the aqueous phase is made isotonic to blood plasma.

27. A pharmaceutical formulation according to Claim 25, wherein the average particle size of the emulsion is from 0.2 to 3.0μm.

28. A pharmaceutical formulation according to claim 25 further comprising an emulsifying agent, a surfactant and/or a pH adjuster.

29. A pharmaceutical formulation according to Claim 1, wherein the CCK antagonist is incorporated into the organic phase and the opioid is incorporated into the hydrophilic phase.

30. A pharmaceutical formulation according to Claim 1, wherein the ratio of component (i) to component (ii) is within the range of 10:1 to 1:5 by weight.

31. A pharmaceutical formulation according to Claim 1, wherein the ratio of component (a) to component (b) is within the range of 1:2 to 1:40 weight.

32. A pharmaceutical formulation according to Claim 1, wherein the CCK antagonist is selected from the group consisting of 3S-(-)-(1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3R-3-(N-(3-methylphenyl)ureido)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

N-[1,3-dihydro-1-methy-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N-[3-(1,2,4-oxodiazol-5-one)phenyl]urea;

(-)-N-[2,3,-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[indan-5-yl]urea; and

[N-[(3R)-5-(3-azabi-cyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-(3-methylphenyl)urea].

33. A pharmaceutical formulation according to Claim 1, wherein the opioid is selected from the group consisting of morphine, codeine, or a salt thereof, and 14-hydroxymorphinan opioid analgesics and salts thereof.

34. A pharmaceutical formulation according to Claim 1 in the form of a solid formulation, an injectable emulsion, a suppository or a tablet.

35. A pharmaceutical formulation according to Claim 1 in a unit dosage form suitable for the delivery of 0.5 to 300mg per day of CCK antagonist to a patient in need thereof.

36. A pharmaceutical formulation according to Claim 35 in unit dosage from suitable for oral use or use as a suppository for the delivery of 1 to 100mg per day of CCK antagonist to a patient in need thereof.

37. A pharmaceutical formulation according to Claim 35 in unit dosage form suitable for intravenous use for the delivery of 1 to 300mg per day of CCK antagonist to a patient in need thereof.

38. A method of treating chronic and neuropathic pain comprising administering to a patient in need thereof a pharmaceutical formulation according to Claim 1.--

Remarks

Prior to the present amendment, Claims 1 and 2 were pending, with Claims 3 to 20 inclusive having been canceled in a preliminary amendment prior to calculation of the filing fee. By the present Amendment, Claims 21 to 38 have been added. The present Amendment does not require payment of a fee inasmuch as the total number of claims does not exceed 20 and the number of independent claims does not exceed 3.

Added Claims 21 to 38 are patterned after the claims pending in applicant's corresponding PCT application as follows.

Attorney Docket No. 24,002 USA
Based on International
Application No. PCT/GB98/03076

April 14, 2000

Claims Added by this Amendment	Pending PCT Claims
21	3
22	4
23	5
24	6
25	7
26	8
27	9
28	10
29	11
30	12
31	13
32	14
33	15
34	16
35	17
36	18
37	19
38	20

An early and favorable Action is requested respectfully.

Respectfully Submitted,

SYNNESTVEDT & LECHNER LLP

Alexis Barron
(Registration No. 22,702)

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COMPOSITIONS

The present invention relates to pharmaceutical formulations suitable for treating pain, in particular, neuropathic pain and/or dysesthesia, and their preparation. In particular, the present invention relates to formulations comprising a cholecystokinin antagonist and an opioid.

Cholecystokinin (hereinafter 'CCK') has been implicated in a variety of physiological functions, one of which is the control of pain. CCK has been shown to have a heterogeneous distribution within the brain, with the greatest levels being found in the hippocampus, cerebral cortex, amygdala and olfactory lobes. The physiological role of central CCK receptors is still under investigation, but it has many of the features of a neurotransmitter. CCK has been found in regions of the brain known to be associated with pain modulation. Furthermore, mole-per-mole, CCK has been found to be much more potent than morphine in tests for analgesia.

However, at variance with these findings, are results of tests which imply that CCK may antagonise endogenous opiate action. (Faris et al. in Science 219 310-2 (1983)). There is evidence that exogenous CCK attenuates analgesia induced by morphine or release of endogenous opioids. These disparate findings and others imply that large doses of CCK induce a 'pharmacological' analgesia whereas small doses of the peptide produce physiological antagonism of opioid analagesics.

CCK also appears to play a rôle in the development of tolerance to opioid analgesia as blockade of CCK receptors has been shown to prevent tolerance to morphine. Hence, blockade of CCK receptors by CCK antagonists may reverse or prevent the development of opiate tolerance in patients, and also potentiates the analgesic effects of opioids. The present invention is therefore based on the thesis that blockage of CCK action may be an effective supplement to morphine (or other opioid) administration in the treatment of chronic pain. However, it is believed that this opioid facilitation is preferentially mediated by the central CCK type B receptors since CCK-B antagonists seem to potentiate the analgesic effects of both opioids and non-

opioids at the spinal level. Furthermore, facilitation of opiate-induced analgesia by CCK-B receptor antagonists seem to be restricted to μ-, rather than d-, opioid receptor-mediated antinociception. Such μ-opioid againsts include morphine and hydroxymethyl fentanyl. However, potentiation of the analgesic effects produced by these opioids has also been observed with (relatively higher doses of) a CCK-A antagonist.

The present invention therefore generally relates to pharmaceutical formulations comprising an opioid-potentiating amount of a CCK antagonist together with an analgesic amount of an opioid. However, although the most popularly-used opioids such as morphine are not difficult to formulate, particularly for administration by injection, as they are water-soluble drugs, many CCK antagonists, particularly the preferred CCK antagonists to which this invention relates, are relatively insoluble compounds which are therefore pharmaceutically incompatible with hitherto-known formulations of opiate drugs. Having therefore taken the step of appreciating the advantages to be gained by co-administration of an opioid with a CCK antagonist in a single formulation, it was then realised that such a formulation, or a satisfactory carrier for the combination of active ingredients, was not available.

The present invention is therefore directed at solving this problem and provides a pharmaceutical formulation comprising

(a) an opioid-potentiating amount of a CCK antagonist;

(b) an analgesic amount of an opioid; and

(c) a pharmaceutically acceptable biphasic carrier comprising

  (i) an organic phase comprising a glyceride derivative; and

  (ii) a hydrophilic phase.

The organic phase may be either solid or liquid at room temperature but preferably has a solubilising capacity for the CCK antagonist in excess of 5mg per gram of organic phase. Examples are oils comprising a glyceride which is liquid at room temperature and glyceride waxes having melting points in the range 35-80°C.

The organic phase may therefore comprise, for example, soya bean,

safflower, sesame, rapeseed, peanut, olive, cotton seed or fish oils. Preferably, soya bean and/or safflower oils are chosen, alone or in combination with glycerine. Alternatively, the organic phase may comprise waxes such as full and/or partial glycerides of fatty acids. Preferably, such waxes are triglycerides and partial glycerides of unsaturated C_{12-18} fatty acids such as, for example, Witepsol H15 or W25.

The hydrophilic phase may itself be aqueous, or may be anhydrous but take in and/or dissolve in water in vivo. In the case of formulations for intravenous use, the hydrophilic phase preferably has a viscosity of from 2500-7500cp (2% aqueous at 20°C), more preferably around 4000cp. Such ingredients may also be added to prevent or reduce coalescence of oily droplets of the organic phase. In the case of solid formulations such as tablets and suppositories, the hydrophilic phase is gel-forming and incorporates the opioid in the gel, and also forms a matrix for incorporating the CCK antagonist plus glyceride. The hydrophilic or aqueous phase may therefore comprise a pharmacologically and pharmaceutically acceptable polymer or salts thereof which may be selected from proteins such as gelatine, hyaluronic acid, alginic acids or salts thereof such as sodium alginate, carboxymethylcellulose (optionally cross-linked), methyl cellulose, other cellulose derivatives which are water-swellable such as hydroxypropylmethyl-cellulose and hydroxyethyl cellulose or other water-swellable polymers such as polyvinyl pyrrolidone (PVP) or water-soluble polymers such as lactose.

In the formulation, the organic and hydrophilic phases may be separated or may be combined, for example, to form an oil-in-water emulsion. Preferred such emulsions therefore comprise:

(i) an oil phase comprising a glyceride derivative; and

(ii) an aqueous phase optionally comprising a buffer whereby the emulsion has a pH of from 6.5 to 7.5 and optionally comprising an isotonicity regulator whereby the aqueous phase is made isotonic to blood plasma.

When the carrier is in the form of an emulsion, the average particle size of the resultant emulsion is preferably in the range 0.2 to 3.0μm, more

preferably around 1μm.

Optionally, an emulsifying agent and/or surfactant may be incorporated into the carrier. A suitable surfactant is a sorbitan derivative such as the polysorbates, for example polysorbate 80, or sorbitan mono-oleate, and the poloxamers such as Pluronic F38. Suitable emulsifying agents include egg yolk lecithin, egg yolk phospholipids such as phosphatidyl choline and the like.

To adjust the pH, a suitable pH adjuster (i.e. an acidifying or alkalising agent) is used such as hydrochloric acid or sodium hydroxide, or a buffer such as a phosphate buffer system. Preferably, the pH is adjusted to 7-7.5, more preferably, it is close to neutral (pH = 7).

Liquid formulations may also comprise an isotonicity regulator to ensure that the aqueous phase thereof is or remains isotonic to blood plasma. Examples of such isotonicity regulators include dextrose, glucose, mannitol, sorbitol, glycerol and sodium chloride.

Other hydrophobic or hydrophilic components may be included in the formulation such as, particularly in the case of suppositories, a thickener or gelling agent for the organic phase such as hydrophobic silicon dioxide or silica; lubricants, particularly in the case of tablet formulations, such as magnesium stearate, stearic acid, talc and LUBITROL, preferably magnesium stearate. Optional other ingredients include colouring or flavouring agents, release agents, pore-forming agents, stabilisers, and fillers or diluents such as lactose, calcium phosphate or carbonate, microcrystalline cellulose and the like, and antioxidants.

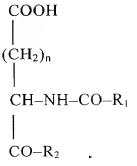
Also, in the case of tablets, a coating may be applied such as waxes, fatty alcohols, water-insoluble cellulose derivatives, other water-insoluble polymers such as polymers or copolymers of acrylates and/or methacrylates (eg. EUDRAGIT), ethylcellulose, cellulose acetate, shellac, hydrogenated vegetable oils and the like. Such a coating may provide the mechanism to enable controlled release of the opioid. Such a coating may optionally include a plasticizer or film enhancer such as monoglycerides, phthalates, sebacates, citrates, castor oil and the like.

Preferably, the CCK antagonist is incorporated into the organic phase, and more preferably into the glyceride derivative, and the opioid analgesic is incorporated into the hydrophilic phase. However, the present invention does not preclude having components (a) and (b) present in any combination in any phase of the carrier.

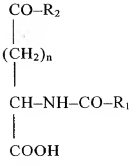
The components are preferably present within the following ranges of ratios: 10:1 to 1:5, respectively (i):(ii); and 1:2 to 1:40, respectively (a):(b).

The opiate drug may be selected from those which are effective analgesics and particularly those which need to be administered at relatively high or increasing doses. Examples include morphine, or a salt thereof such as the sulphate, chloride or hydrochloride, or other 14-hydroxymorphinan opioid analgesics such as naloxone, meperidine, butorphanol or pentazocine, or morphine-6-glucuronide, codeine, dihydrocodeine, diamorphine, dextropropoxyphene, pethidine or fentanyl, or a salt of any of these.

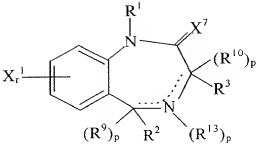
The CCK antagonist may be selected from any of those which potentiate the analgesic effects of the opioid chosen and/or which reverse or prevent patient tolerance thereto. For example, CCK antagonists include those of formulae (I)-(IV) which are defined, respectively, in (I) US 4791 215; (II) EPs 167 919 and 284 256; (III) EP 405 537; and (IV) J. Med. Chem. 34 1508 (1991), which are herein incorporated by reference in their entirety.



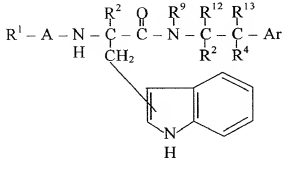
(Ia)



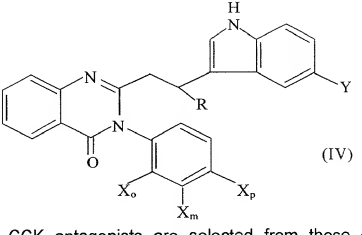
(Ib)



(II)



(III)



(IV)

Preferred CCK antagonists are selected from those described in European patents specifications nos. 167 919; 284 256; 508 796; 652 871; 411 668; 421 802; and 617 621, which are herein incorporated by reference in their entirety. Particularly preferred CCK antagonists include devazepide (also known as MK-329), namely, 3S-(-)-(1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (a CCK-A antagonist); L-365,260, namely 3R-3-(N'-(3-methylphenyl)ureido)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (a CCK-B

antagonist); and so-called second generation compounds such as L-369,466, namely N-[1,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N'-[3-(1,2,4-oxodiazol-5-one)phenyl]urea, L-741,528, namely (-)-N-[2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[indan-5-yl]urea and [N-[(3R)-5-(3-azabi-cyclo [3,2,2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-(3-methylphenyl) urea] (L-740,093, a CCK-B antagonist described in Molecular Pharmacol. 46 943-8 (1994)). Especially preferred are the CCK-B antagonists, in particular L-365,260 and the previously-mentioned second generation compounds.

The formulations of the present invention are preferably sustained-, slow- or continuous-release (S.R.) solid formulations, or emulsions for injection. S.R. formulations may be in the form of a suppository or tablet, for example.

The formulations of the present invention are particularly suitable for treating chronic and neuropathic pain. Nerve damage arising from either trauma or disease affecting peripheral nerves leads to abnormal pain states referred to as neuropathic pain. Such pain may be long-lasting and continue for extended periods after the initial injury has healed. Individuals afflicted with neuropathic pain show a marked sensitivity to nociceptive stimuli, indicative of a lowered nociceptive threshold (hyperalgesia). Moreover, there is also a perception of normally innocuous stimuli being nociceptive, a state referred to as allodynia.

In particular, these formulations are suitable for treating patients with spinal cord injury. They prevent tolerance to the opioid analgesic and eliminate the need to increase doses of opioid to clinically unacceptable levels. However, they are also useful in enhancing opioid analgesia in non-pathological pain states, and the anxiolytic (anti-anxiety or anti-panic) effects of some CCK antagonists is a particularly beneficial additional effect.

A suitable daily dose or CCK antagonist in these formulations would preferably be in the range 0.5 to 300mg per day, such as 1 to 100mg/day (oral or via suppository) or 1 to 300mg/day (i.v.). Preferably, for MK-329, the

dose would be 1-10mg/day (5-10 mg/day orally or 1-3mg/day i.v.); for L-365,260, the dose would be 10-100mg/day orally (5-10mg/day orally or 10-300 mg/day i.v.); and for 'second generation' CCK antagonists, 1-2mg/day (oral) or 0.5-1.5 mg/day (i.v.).

The present invention will now be illustrated by the following non-limiting examples:

Example 1 : Intravenous Emulsions

(a)	L-740,093 (active (a))	0.00025g
	Morphine sulphate (active (b))	0.010g
	Soya bean oil (i)	0.4000ml
	Phosphatidyl choline (emulsifier)	0.0240g
	Pluronic F 68 (surfactant)	0.0040g
	Water (ii)(adjusted to pH 7 to 7.5 and made isotonic with sorbitol q.s.)	2ml

The injection is prepared using aseptic techniques and sterile materials. The MK-329 is dispersed in the soya bean oil and the morphine is dissolved in the water. The two phases are emulsified using standard pharmaceutical technology and stabilised by the phosphatidyl choline and Pluronic F 68. The amount of morphine sulphate may be altered to provide a range of potencies. A 2ml bolus intravenous injection may be administered every four hours, or the formulation may be incorporated into the reservoir of an analgesic self-administration device.

			1g =~ 1ml
(b)		MK-329 (a)	0.0015g
		Fentanyl citrate (b)	0.0024g
		Soya bean oil (i)	0.0993g
		Safflower oil (i)	0.0993g
		Phosphatidyl choline (emulsifier)	0.0125g
		Glycerine	0.0200g
		Water (qs 1 ml) (ii)	0.7665g
		qs 0.1 N NaOH to adjust pH to 7.0 - 7.5	

The ingredients were mixed together and emulsified in a similar manner to that described above in Example 1(a).

Example 2 : Intravenous Infusions

(a)	MK-329 (a)	0.015g
	Morphine sulphate (b)	0.100g
	Cottonseed oil (i)	200ml
	Polysorbate (surfactant)	1.6g
	Fractionated egg phospholipids (emulsifier)	12.000g
	Hydroxypropyl methylcellulose (ii)	5.000g
	Water (ii) (adjusted to pH 7 to 7.5 and made isotonic with sorbitol)	1000ml

The MK-329 is dispersed in the oil phase and the fentanyl citrate is dispersed in the aqueous phase. The emulsion is formed using standard pharmaceutical techniques. One litre of emulsion may be adminstered intravenously over a 24-hour period. The amount of morphine may be adjusted to allow a range of doses, depending on the response of individual patients.

(b)	L-365,260 (a)	0.03g
	Morphine sulphate (b)	200mg
	Soya bean oil (i)	100g
	Egg yolk lecithin (emulsifier)	12g
	Glycerine (i)	25g
	Gelatine (ii)	50 g
	Water q.s. to (ii)	1 litre

All the ingredients are emulsified together, except the gelatine, at 80°C. The temperature is reduced to about 40°C and the gelatine added.

Example 3 : S.R. Suppository

Butorphenol tartrate (b)	30mg
MK-329 (a)	12mg
Hydroxypropyl methylcellulose (ii)	300mg

Aerosil R972* (thickener)	100mg
Witepsol H15 or ((i), glycerides)	
Witepsol W25 to	2500mg

(*Hydrophobic silica)

The MK329 and Aerosil are added to molten Witepsol. The butorphenol is blended with hydroxypropyl methylcellulose and then added to the Witepsol mixture. The mixture is poured into 3 ml moulds and shock cooled to room temperature.

Example 4 : Coated S.R. Tablet

(a)	Core	
	MK-329 (a)	0.015g
	Suppocire DM (((i), glyceride*)	0.100g
	Levorphanol tartrate (b)	0.006g
	Crosslinked polyvinyl	
	pyrrolidone (PVP) (ii)	0.010g
	Lactose (ii)	0.175g
	Coating	
	Cellulose acetate	0.020g
(b)	Core	
	Dihydrocodeine tartrate (b)	180mg
	Suppocire DM ((i), glyceride)	100mg
	L-741,528 (a)	4mg
	Polyvinylpyrrolidone (PVP) (ii)	40mg
	Lactose (ii)	123mg
	Magnesium stearate (lubricant)	1.5mg

* Suppocire DM is a mixture of hemi-synethetic glycerides of C_{12-18} saturated with fatty acids.

Coating	
Hydroxypropyl methylcellulose (ii)	14.45mg
Triethyl citrate (plasticiser)	6.9mg
30% aqueous dispersion	
ethyl cellulose	17.21mg

Purified water	q.s.

The dihydrocodeine tartrate is dispersed in molten Suppocire which is cooled with constant stirring to give a granular product. These granules are blended with other materials and tableted.

Example 5 : S.R. Tablet

L-740,093 (a)	0.002g
Suppocire DM ((i), glyceride)	0.100g
Dihydrocodeine tartrate (b)	0.180g
Magnesium stearate (lubricant)	0.003g
Hydroxypropyl methyl cellulose (ii)	0.250g
	0.548g

The L-740,093 is dissolved in molten Witepsol W25 at 50-60°C. The resulting liquid is atomised into a chamber containing chilled nitrogen (gas) at about 10°C. Spherical particles produced thereby are in the range 80-120 µm. These are then blended with the dihydrocodeine tartrate and remaining excipients to produce a powder which is tabletted by standard techniques.

Example 6 : S.R. Capsules

L-369,466 (a)	0.0004g
Morphine sulphate (b)	0.100g
Suppocire DM ((ii), glyceride)	0.200g
Sodium alginate (i)	0.200g

The L-369,466 and morphine are incorporated into molten Witepsol. Granules or spheroids are produced by standard pharmaceutical techniques, then blended with the sodium alginate before filling into capsule shells. The amount of morphine in each capsule, for once daily administration, can be changed within the range 30mg to 150mg.

CLAIMS

1. A pharmaceutical formulation comprising

(a) an opioid-potentiating amount of a CCK antagonist;

(b) an analgesic amount of an opioid; and

(c) a pharmaceutically acceptable biphasic carrier comprising

(i) an organic phase comprising a glyceride derivative; and

(ii) a hydrophilic phase.

2. A pharmaceutical formulation according to claim 1, wherein the organic phase (i) has a solubilising capacity for the CCK antagonist in excess of 5mg per gram of organic phase.

3. A pharmaceutical formulation according to claim 1 or 2, wherein the organic phase comprises an oil selected from soya bean, safflower, sesame, rapeseed, peanut, olive, cotton seed and fish oils, alone or in combination with glycerine and/or a wax selected from full and/or partial triglycerides of fatty acids.

4. A pharmaceutical formulation according to any one of claims 1 to 3, intended for intravenous use, wherein the hydrophilic phase is aqueous and has a viscosity of from 2500-7500cp at 20°C.

5. A pharmaceutical formulation according to any one of claims 1 to 3, intended for use as a solid formulation, wherein the hydrophilic phase is gel forming, incorporates the opioid in the gel and forms a matrix incorporating the CCK antagonist and the glyceride derivative.

6. A pharmaceutical formulation according to any one of the preceding claims wherein the hydrophilic phase comprises a pharmacologically and pharmaceutically acceptable polymer or salt thereof selected from proteins such as gelatine, hyaluronic acid, alginic acids or salts thereof such as sodium alginate, carboxymethylcellulose (optionally cross-linked), methyl cellulose, other cellulose derivatives which are water-swellable such as hydroxypropylmethylcellulose and hydroxyethyl-cellulose or other water-swellable polymers such as polyvinyl pyrrolidone (PVP) or water-soluble

polymers such as lactose.

7. A pharmaceutical formulation according to any one of the preceding claims, wherein the carrier is in the form of an oil-in-water emulsion.

8. A pharmaceutical formulation according to claim 7, wherein the oil-in-water emulsion comprises

(i) an oil phase comprising a glyceride derivative; and

(ii) an aqueous phase optionally comprising a buffer whereby the emulsion has a pH of from 6.5 to 7.5 and optionally comprises an isotonicity regulator whereby the aqueous phase is made isotonic to blood plasma.

9. A pharmaceutical formulation according to claim 7 or 8 wherein the average particle size of the emulsion is from 0.2 to 3.0μm.

10. A pharmaceutical formulation according to any one of claims 7 to 9 further comprising en emulsifying agent, a surfactant and/or a pH adjuster.

11. A pharmaceutical formulation according to any one of the preceding claims, wherein the CCK antagonist (a) has been incorporated into the organic phase (i) and the opioid analgesic (b) has been incorporated into the hydrophilic phase (ii).

12. A pharmaceutical formulation according to any one of the preceding claims, wherein the ratio of component (i) to component (ii) is within the range of 10:1 to 1:5 by weight.

13. A pharmaceutical formulation according to any one of the preceding claims, wherein the ratio of component (a) to component (b) is within the range of 1:2 to 1:40 by weight.

14. A pharmaceutical formulation according to any one of the preceding claims, wherein the CCK antagonist (a) is selected from:

3S-(-)-(1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3R-3-(N′-(3-methylphenyl)ureido)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

N-[1,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N′-[3-(1,2,4-oxodiazol-5-one)phenyl]urea;

(-)-N-[2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N´-[indan-5-yl]urea; and
[N-[(3R)-5-(3-azabi-cyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N´-(3-methylphenyl)urea].

15. A pharmaceutical formulation according to any one of the preceding claims, wherein the opioid (b) is selected from morphine, codeine, or a salt thereof, and 14-hydroxymorphinan opioid analgesics and salts thereof.

16. A pharmaceutical formulation according to any one of the preceding claims as a solid formulation, an injectable emulsion, suppositories or tablets.

17. A pharmaceutical formulation according to any one of the preceding claims in unit dosage form suitable for the delivery of 0.5 to 300mg per day of CCK antagonists to a patient in need thereof.

18. A pharmaceutical formulation according to claim 17 in unit dosage form suitable for oral use or use as a suppository for the delivery of 1 to 100mg per day of CCK antagonist to a patient in need thereof.

19. A pharmaceutical formulation according to claim 17 in unit dosage form suitable for intravenous use for the delivery of 1 to 300 mg per day of CCK antagonist to a patient in need thereof.

20. A method of treating chronic and neuropathic pain comprising administering to a patient in need thereof a pharmaceutical formulation according to any one of the preceding claims.

ABSTRACT

Pharmaceutical formulations, particularly suitable for treating chronic and neuropathic pain comprise an opioid-potentiating amount of a CCK antagonist and an analgesic amount of an opioid in a pharmaceutically acceptable biphasic carrier comprising an organic phase comprising a glyceride derivative and a hydrophilic phase.

Docket No.
24,002 USA

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

ANALGESIC COMPOSITIONS

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on **October 12, 1998** as United States Application No. or PCT International Application Number **PCT/GB98/03076**

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
97-21746.7	**United Kingdom**	**15/10/97**	☐
(Number)	(Country)	(Day/Month/YearFiled)	
			☐
(Number)	(Country)	(Day/Month/YearFiled)	
			☐
(Number)	(Country)	(Day/Month/YearFiled)	

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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